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Sterile filtration of large biomolecules - New insights using live attenuated vaccines and model particle suspensions

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STERILE FILTRATION OF LARGE BIOMOLECULES – NEW INSIGHTS USING LIVE ATTENUATED VACCINES AND MODEL PARTICLE SUSPENSIONS

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Sterile filtration is widely used among manufacturers to sterilize vaccine antigens, utilizing 0.2 µm nominal pore size membranes to remove all bacteria. Incorporation of a sterile filtration step significantly reduces manufacturing burden by eliminating the need for a fully aseptic end-to-end manufacturing process. Although the sterile filtration of recombinant proteins is relatively straightforward, live attenuated viral (LAV) vaccines with large particle sizes (100 – 400 nm) pose significant challenges during sterile filtration, specifically low yields and capacities. Experimental studies were performed with both an LAV and a model particle system. Small differences in the average pore size of sterile filters (determined by mercury porosimetry) had a large effect on the particle transmission, with the Sartobran P (average pore size of 0.46 µm) having more than 80% viral particle yield while the Millipore Express SHF (average pore size of 0.33 µm) had a particle yield of <1%. In addition, the filter capacity and particle yield could be significantly increased using appropriate prefilters due to selective removal of larger particles in the feed suspension. Confocal and scanning electron microscopy were used to directly evaluate the extent and location of foulant capture within both the prefilter and sterile filters. This work provides important insights into the factors controlling sterile filtration of large particle vaccines and enables sterile filtration of vaccine products previously assumed to be too large for sterile filtration. The work also provides a framework for enhancing the yield and capacity of commercially available sterile filters.